Jonathan D. Moreno, Ph.D.
Center for Biomedical Ethics

Book of Daniel

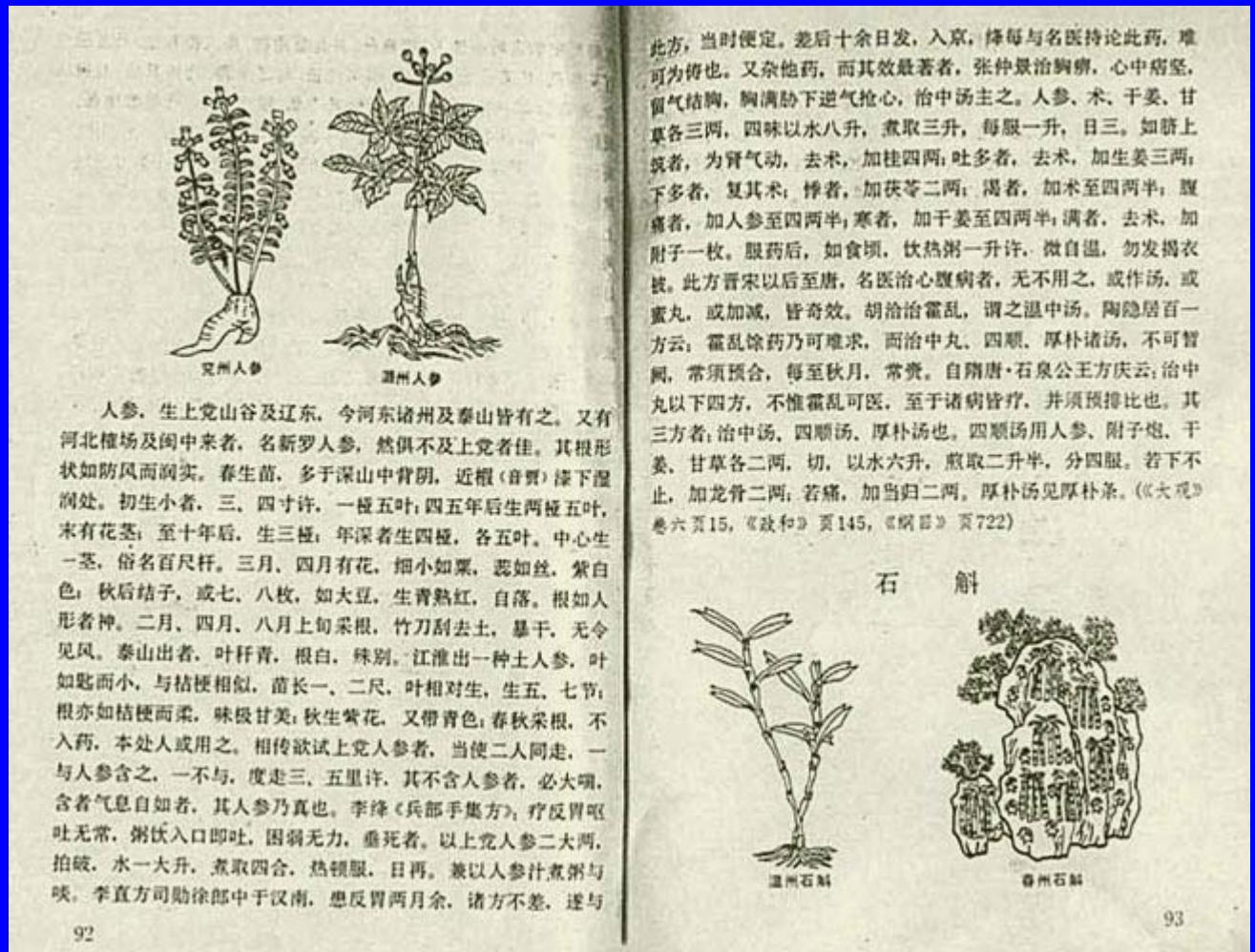
Now Daniel determined not to contaminate himself by touching the food and wine assigned to him by the (Chaldean) king, and he begged the master of the eunuchs not to make him do so. …Then Daniel said to the guard whom the master of the eunuchs had put in charge of Hananiah, Mishael and Azariah and himself 'Submit us to this test for ten days.

Give us only vegetables to eat and water to drink; then compare our looks with those of the young men who have lived on the food assigned by the king and be guided in your treatment of us by what you see.'

The guard listened to what they said and tested them for ten days.

At the end of ten days they looked healthier and were better nourished than all the young men who had lived on the food assigned them by the king.

Ben Cao Tu Jing (1061). (Atlas of Materia Medica). Song Dynasty (960-1279).



兖州人参　　潞州人参

人参，生上党山谷及辽东，今河东诸州及泰山皆有之。又有河北槽场及闽中亲者，名新罗人参，然俱不及上党者佳。其根形状如防风而润实。春生苗，多于深山中背阴，近根（音贾）壤下湿润处。初生小者，三、四寸许，一梗五叶；四五年后生两梗五叶，末有花茎；至十年后，生三梗；年深者生四梗，各五叶。中心生一茎，俗名百尺杆。三月、四月有花，细小如粟，蕊如丝，紫白色；秋后结子，或七、八枚，如大豆，生青熟红，自落。根如人形者神。二月、四月、八月上旬采根，竹刀刮去土，暴干，无令见风。泰山出者，叶纤青，根白，殊别。江淮出一种土人参，叶如匙而小，与桔梗相似，苗长一、二尺，叶相对生，生五、七节；根亦如桔梗而柔，味极甘美；秋生紫花，又带青色；春秋采根，不入药，本处人或用之。相传欲试上党人参者，当使二人同走，一与人参含之，一不与，度走三、五里许，其不含人参者，必大喘，含者气息自如者，其人参乃真也。李绛《兵部手集方》：疗反胃呕吐无常，粥饮入口即吐，困弱无力，垂死者。以上党人参二大两，拍破，水一大升，煮取四合，热顿服，日再。兼以人参汁煮粥与啖。李直方司勋徐郎中于汉南，患反胃两月余，诸方不差，遂与

92

北方，当时便定。差后十余日发，入京，绛每与名医持论此药，堪可为俦也。又杂他药，而其效最著者，张仲景治胸痹，心中痞坚，留气结胸，胸满胁下逆气抢心，治中汤主之。人参、术、干姜、甘草各三两，四味以水八升，煮取三升，每服一升，日三。如脐上筑者，为肾气动，去术，加桂四两；吐多者，去术，加生姜三两；下多者，复其术；悸者，加茯苓二两；渴者，加术至四两半；腹痛者，加人参至四两半；寒者，加干姜至四两半；满者，去术，加附子一枚。服药后，如食顷，饮热粥一升许，微自温，勿发揭衣被。此方晋宋以后至唐，名医治心腹病者，无不用之，或作汤，或蜜丸，或加减，皆奇效。胡治治霍乱，谓之温中汤。陶隐居百一方云：霍乱诠药乃可难求，而治中丸、四顺、厚朴诸汤，不可暂阙，常须预合，每至秋月，常贵。自隋唐·石泉公王方庆云：治中丸以下四方，不惟霍乱可医，至于诸病皆疗，并须预排比也。其三方者：治中汤、四顺汤、厚朴汤也。四顺汤用人参、附子炮、干姜、甘草各二两，切，以水六升，煎取二升半，分四服。若下不止，加龙骨二两；若痛，加当归二两。厚朴汤见厚朴条。（《大观》卷六页15，《政和》页145，《纲目》页722）

石　斛

温州石斛　　寿州石斛

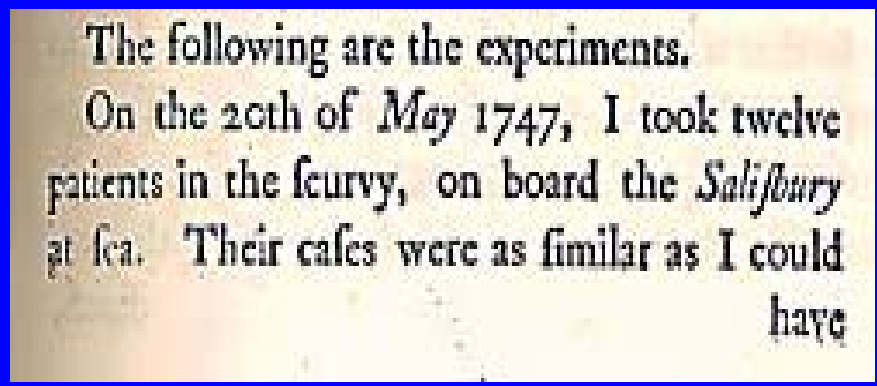
93

The *Ben Cao Tu Jing (Atlas of Materia Medica), 1061*

Central government ordered collection of specimens from throughout the country thought to possess medicinal properties--plants, animals, and minerals. Nearly one thousand samples were collected, documented for alleged therapy, etc.

James Lind and the HMS Salisbury, 1753

- **Compared 6 treatments for scurvy in 12 patients; endorsed fresh fruit for sailors**
- **Not adopted by Royal Navy for 42 years**



The following are the experiments.

On the 20th of *May* 1747, I took twelve patients in the ſcurvy, on board the *Saliſbury* at ſea. Their caſes were as ſimilar as I could have

Controlling for Bias

- **1784--Ordered by Louis XVI to investigate claims of "animal magnetism," Ben Franklin blindfolded subjects who were told or not told they were being remotely healed; subjects only reported receiving magnetism when they were told they were, even if they weren't**
- **1800--Haygarth showed that fake tractors made of wood were just as "healing" as metal tractors.**
- **1830-40s—experiments on homeopathic claims using sugar pills and double-blinded.**
- **1930s—placebo controls become popular in German and English-speaking worlds, following popularity for revealing medical quackery.**

Henry K. Beecher, "The Powerful Placebo," JAMA, 1955

- Beecher reviewed 26 studies and found that an average of 32 percent of patients responded to placebo

- Beecher's other famous paper: "Ethics and Clinical Research," NEJM, 1966

Henry Beecher

NEJM paper, 1966

- **Brooklyn Jewish Chronic Disease Hospital**
- **Willowbrook State Hospital**

Rejected “rigid rules” in favor of the “virtuous investigator”

USPHS Syphilis Study, 1932-72

(Courtesy National Archives)

The study lasted nearly 40 years
(Courtesy National Archives)

The Belmont Report (1979)

- Distinguish research from therapy
- Principles
  - Respect for persons
  - Beneficence (non-maleficence)
  - Justice
    - National Commission for Protection of Human Subjects of Biomedical and Behavioral Research

45CFR.46 Protection of Human Subjects (DHHS)

- Part A is the Common Rule for 17 Federal agencies (1991)

- Parts B,C,D for “vulnerable populations”:
  - B: Fetuses, pregnant women, infants of uncertain viability
  - C: Prisoners
  - D: Children

Central concepts of common rule

- IRB review—need not be local IRB
- Exempt research—e.g., educational tests, unlinked biomaterials from public sources
- Expedited review—e.g., minimal risk
- Informed consent
- Parent or legal guardian

The “Double Agent” Problem and Equipoise

- Clinical trials require the therapist to take the role of scientist (the “double agent’)
- How can that be consistent with the role-related duties of the therapist?
- Equipoise is supposed to resolve this problem

Theoretical Equipoise

- “Overall, the evidence in favor of two treatment regimens is exactly balanced” (Freedman)
- Evidence may be derived from a variety of sources, from basic science to gut feeling
- Very fragile

Principle of Clinical Equipoise

A *genuine uncertainty* on the part of the *expert medical community* about the *comparative therapeutic merits* of each arm of a clinical trial

Clinical Equipoise

- “[a]t the start of the trial there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way to make it reasonable to expect that, if it successfully conducted, clinical equipoise will be disturbed.”

  » Benjamin Freedman

Clinical Equipoise

- Provides the conceptual foundation for the requirement that the health of subjects not be *disadvantaged* by research participation (beneficence/non-maleficence)
- Unlike theoretical equipoise, clinical equipoise is robust (reluctance of surgeons to participate in clinical trials)

Regulatory status

- **Although not specifically required, the Food and Drug Administration seems generally to regard a placebo-controlled clinical trial as the methodologic "gold standard"**

- **No *a priori* bar to placebo controlled trials in populations identified in federal regulations as vulnerable (pregnant women, fetuses, prisoners, children), but look to regulations for specifics**

Clinical Trials

- Phase II and III studies often include a placebo control to detect and quantify the acute toxicity and efficacy of an experimental drug
- The use of placebos can create a conflict between the duty to *maximize* the benefit to subjects and *minimize* harm

Therapeutic Misconception

- However, *there is no duty on the part of researchers to benefit subjects*
- If this were the case then research would be clinical medicine
- To fail to understand the difference is to fall victim to the “therapeutic misconception”
- The risk of harm to subjects must be minimized, but can never be eliminated

Cancer Patients (n=240) and the Therapeutic Misconception

- 70 percent did not realize that the treatment being studies had not been proven to be the best cancer treatment
- Many did not understand that they might not receive any direct medical benefit from their participation or that the purpose of a clinical trial was to benefit future patients, not themselves
- More than half of physicians did not realize that the goal of trials was to benefit future patients (Lancet 2001, 358)

When Placebo Controls May be Used

- There is no standard treatment
- Standard treatment has been shown to be no better than placebo
- Evidence causes doubt about therapeutic advantage of standard therapy

When Placebo Controls May be Used: Controversial Conditions

- Many argue that persons with conditions with a low risk of harm (understand as low *probability* or low *magnitude* of harm) may be entered into a placebo arm

- Many argue that placebo controls are ethical when resources are limited and standard treatment is not available

When Placebo Controls May be Used

- In a population of patients who are refractory to standard treatment and for whom there is no standard second-line treatment
- Testing add-on treatment to standard therapy when all subjects in the trial receive all treatments that would normally be prescribed

The perinatal AZT trial in Thailand

- **Could a shorter and cheaper course of AZT prevent perinatal transmission?**
- **Harvard group, NIH funded**
- **Double-blind, placebo controlled**
- **Was placebo control ethical?**

Declaration of Helsinki (prior to 2000)

- In any medical study, every patient--including those of the control group, if any--should be assured of the best *proven* diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists (emphasis added).

Declaration of Helsinki (2000)

- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best *current* prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, and therapeutic method exists (emphasis added).

Declaration of Helsinki (October 2002 statement)

- ... a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method, or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

Informed Consent

- Subjects or legal representatives must be informed
  - **of the likelihood that they will be randomly assigned to a placebo group**
  - **consequences of withholding treatment**
  - **reasons why a placebo-controlled trial is deemed to necessary**

How Effective is Informed Consent?

- **Informed consent as episode and as process**
- **Episodic informed consent: Lit suggests that a day later half remember one fact (comprehension vs. memory).**
- **Re-consenting should be considered, esp. for longer studies**
- **Subject Interview Study (1995): 8% didn't know they were in research; 30% thought they were but were not (n=1900)**
  - **Advisory Committee on Human Radiation Experiments**

Placebo Controls, Informed Consent and Persons Who Lack Decision Making Capacity

- **In general, legally authorized representatives do not have the authority to permit research participation in trials that do not present the prospect of direct benefit**
- **An exception appears to be California, due to recent legislation that appears to allow surrogates to consent to research participation without qualification by level of risk**

Compensation/Justice

- In some instances subjects may be offered the opportunity to receive the experimental drug *gratis* for some period if they are in the placebo arm and if the results of the study disturb equipoise in favor of the experimental arm

Placebo-Controlled Sham Surgery Trials

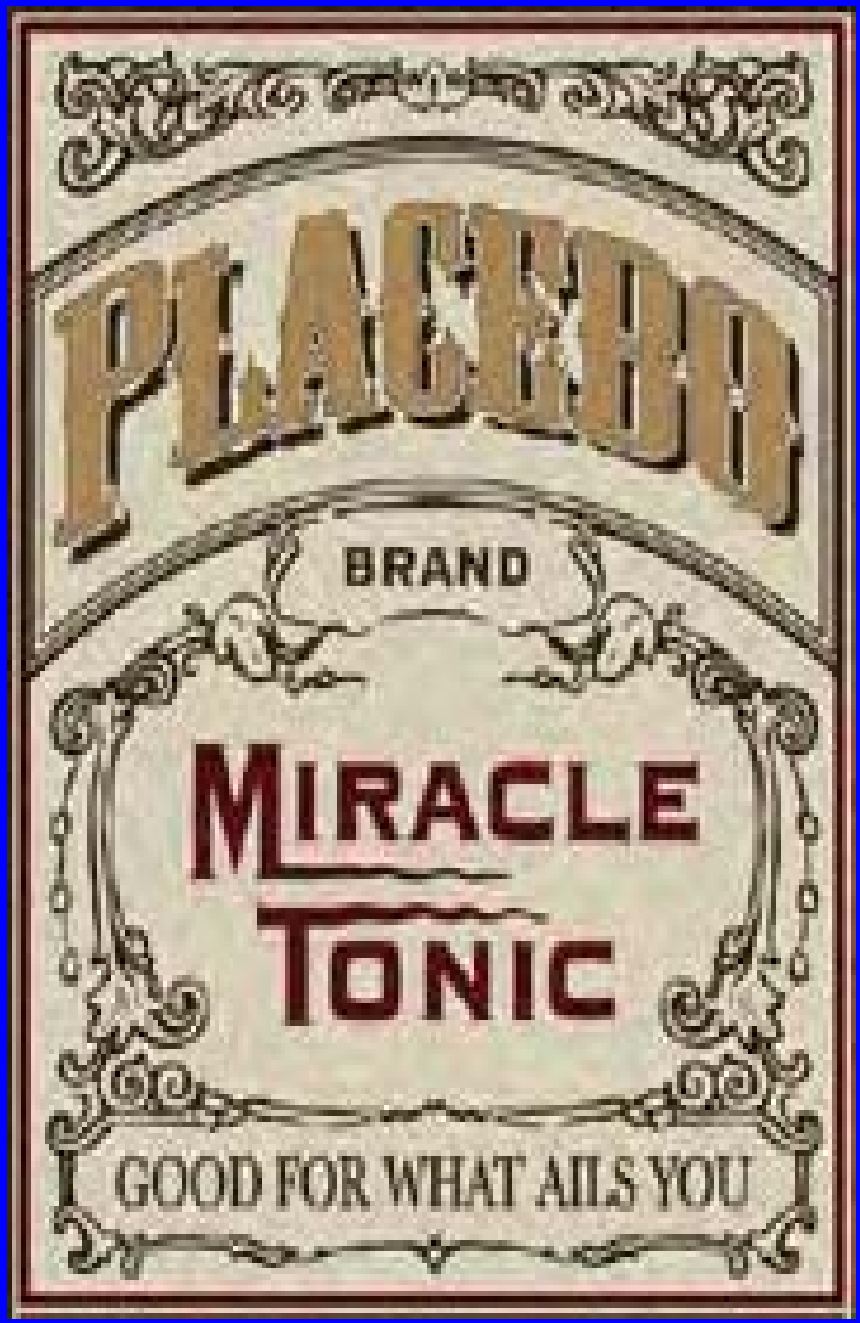
- Fetal tissue neuroimplants for Parkinson's
- Arthroscopic knee surgery for arthritis
- Spine-fusion surgery for osteoporosis

Data Safety Monitoring Boards

- Have access to blinded study data
- Have authority to issue “stop” orders
- Are multidisciplinary
- Increasingly utilized in both NIH and privately sponsored studies
- Relationship with IRB is an issue

A Rarely Discussed Issue: Data Safety Monitoring Boards and Equipoise

- If the DSMB is at some point cannot agree about whether, *based on the direction of the data alone*, the two arms of a study present equivalent risks, what should the default position be?
  - Continue the study until the data make possible a more confident judgment
  - Discontinue the study
  - Inform subjects of the results that may be emerging


PLACEBO
BRAND
MIRACLE
TONIC
GOOD FOR WHAT AILS YOU